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Original Study

Effects of an Oral Nutritional Supplementation Plus Physical Exercise Intervention on the Physical Function, Nutritional Status, and Quality of Life in Frail Institutionalized Older Adults: The ACTIVNES Study

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A B S T R A C T

Objectives: The objective of this study was to assess the effects of a hyperproteic, hypercaloric oral nutritional supplement with prebiotic fiber, vitamin D, and calcium, plus a standardized physical intervention, in the functional status, strength, nutritional status, and quality of life of frail institutionalized older adults.
Design: Multicentric prospective observational study under usual clinical practice conditions.
Setting: Four nursing homes from Burgos (2), Albacete, and Madrid, Spain.
Participants: Participants included 91 institutionalized older adults (age ≥70), able to walk 50 m, and meeting at least 3 of the Fried frailty phenotype criteria.
Intervention: Daily intake of two 200-mL bottles of an oral nutritional supplement, each bottle containing 300 kcal, 20 g protein, 3 g fiber, 500 IU vitamin D, and 480 mg calcium, plus a standardized physical exercise training consisting of flexibility, balance, and strengthening exercises for arms and legs, 5 days per week.
Measurements: Short Physical Performance Battery (SPPB), Short-Form-Late-Life Function and Disability Instrument (SF-LLFDI) function subscale, handgrip strength, EuroQoL-5 Dimensions visual analogic scale (EQ5DVAS), weight, body mass index (BMI), and Short-Form Mini Nutritional Assessment (MNA-SF) at baseline and 6 and 12 weeks.
Results: Forty-eight participants (52.7%) improved at least 1 point in the SPPB at week 6, and 44 (48.4%) did so at week 12; 39 participants (42.9%) improved at least 2 points in the SF-LLFDI at week 6, and 46 (50.5%) at week 12. Participants improved their quality of life measured with the EQ5DVAS by 6% (95% confidence interval [CI] 3%–10%) at week 6, and by 5% (95% CI 0%–10%) at week 12. They also improved their nutritional status (weight gain, BMI increase, and higher MNA-SF scores at 6- and 12-week follow-up). This improvement was higher in participants with more frailty criteria, lower functional level, lower vitamin D levels, and poorer nutritional status.
Conclusion: A 12-week intervention with oral nutritional supplementation plus physical exercise improves function, nutritional status, and quality of life in frail institutionalized older adults.

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Physical frailty is a medical syndrome with multiple causes and contributors that is characterized by diminished strength, endurance, and reduced physiologic function that increases an individual's vulnerability for developing increased dependency and/or death.[1,2] Frailty is a common syndrome in community-dwelling older adults, with a pooled prevalence of 10.7% in more than 60,000 individuals.[3] However, there are few studies that have analyzed these data in institutionalized older adults, yielding a prevalence between 34.9% and 68.8%.[4–8] Frailty has been associated with health-related adverse events like mortality,[9] disability in basic activities of daily living (BADLs), and mobility disability,[10] hospitalization, institutionalization, and falls in community-dwelling older adults,[11] and recently the association between frailty and incident mortality or disability in BADLs in institutionalized older adults also has been demonstrated.[12,13]

Although frailty is a high prevalent condition associated with adverse events in institutionalized older adults, few interventions have focused on this target population. It is well known that exercise and nutrition are effective interventions in frail community-dwelling older adults. Oral nutritional supplementation has a grade A recommendation from ESPEN (European Society for Clinical Nutrition and Metabolism) to improve or maintain nutritional status in frail older adults,[14] and exercise has been associated with many benefits in this population, including decrease/delay in frailty development, increase in physical fitness and strength, lower incidence of sarcopenia, lower incidence of functional loss, better "brain health," better repair of musculoskeletal injuries, increase in quality of life and function, decrease in falls risk and incidence, increase in bone mineral density, better gait and balance, and a 30% decrease in all-cause mortality and morbidity.[15–18]

In institutionalized older adults, physical exercise has demonstrated to improve function as measured with the Barthel index, the Rivermead Mobility Index, and the Timed Up and Go test, and it also has been associated with a beneficial effect on strength, flexibility, and balance, and possibly on mood. However, mean effects are small, and may not be applicable to all residents.[19–21] Regarding nutritional supplementation, protein supplementation has been associated with improvement in physical performance in frail older adults,[22] and with muscle mass increase when combined with resistance exercise.[23] Moreover, low vitamin D levels have been associated with increased mortality in nursing home residents,[24,25] and supplementation in this population has been associated with a reduced rate of falls.[26]

Despite the evidence presented, there are few studies with both physical exercise plus nutrition intervention in this population,[27,28] and no specific studies to analyze if a combined intervention of physical exercise plus nutritional supplementation enriched with vitamin D, calcium, and fiber, in frail institutionalized older adults, would improve functional and nutritional status, and quality of life. This was the reason to design the ACTIVNES study.

Methods

Objective

The main objective was to assess the effects of a hyperproteic, hypercaloric (HP/HC) oral nutritional supplement (ONS) with prebiotic fiber, vitamin D, and calcium, plus a standardized physical intervention, in the functional status, strength, nutritional status, and quality of life of frail institutionalized older adults in Spain, under usual clinical practice conditions.

Design

This was a multicentric prospective observational study under usual clinical practice conditions in 4 institutions from Spain ($n = 91$). The 4 institutions were "Residencia Jardín" and "Residencia de mayores Fuentes Blancas," both in Burgos, "Residencia ORPEA Group San Blas" in Madrid, and "Residencia de Mayores Núñez de Balboa" in Albacete.

Population

Inclusion criteria were patients 70 years or older, able to walk 50 m, and living in one of the institutions previously described. Patients had to meet at least 3 of the Fried frailty phenotype criteria as originally proposed by the author with the same cut points (unintentional weight loss over 4.5 kg or 5% in the past year, exhaustion in the past week, slow walking speed, low physical activity, and low handgrip strength). Participants had to be able to accomplish a daily physical exercise plan, and they had to be already taking for less than 3 weeks or starting to take an HP/HC nutritional formula with prebiotic fiber, vitamin D, and calcium. Written informed consent was necessary before enrollment in the study.

Intervention

ONS (Resource Senior Activ; Nestlé Health Science-NHS, Barcelona, Spain) consisted of daily intake of 2 bottles of 200 mL. Each bottle contains 300 kcal, 20 g protein, 24.2 g carbohydrate, 13 g fat (polyunsaturated fatty acids 18.5%; $\omega_6/\omega_3 = 2.8{:}1$), 3 g fiber (30% inulin, 70% fructooligosaccharides), 500 IU vitamin D, and 480 mg calcium. Intake was calculated to increase 30% of daily kilocalories.

Standardized physical exercise training (ActiPlan; Nestlé Health Science-NHS) is presented in Figure 1. It was conducted 5 days per week and was supervised by physiotherapists. After evaluation of the ability to perform physical exercise, flexibility, balance, and strengthening exercises for arms and legs were prescribed. There was a safety assessment plan, and a daily adherence evaluation plan. Every 2 weeks there was an evaluation of progression, measuring volume, intensity, and number of repetitions.

Outcome Variables

All outcome variables were measured at baseline and at weeks 6 and 12, except blood sample parameters that were recorded only at baseline and at 12-week follow-up.

The Short Physical Performance Battery (SPPB) is a questionnaire of 5 items and 3 dimensions: balance, walking speed, and time to stand up from a chair 5 times. Score ranges from 0 (poor performance) to 12 (best performance).[29] Participants were classified as poor function (0–3 points), intermediate function (4–7 points), and high function (8–12 points). We considered the minimal clinical important difference (MCID) an increase of 1 point between baseline and follow-up data.[30]

The Spanish version of the Short-Form-Late-Life Function and Disability Instrument (SF-LLFDI), function subscale, is a 15-item questionnaire to assess functional limitations in older adults. Score ranges from 15 (high functional limitation) to 75 (absence of functional limitation).[31] Although there are no data regarding the MCID for this test,[32] we considered an increase of 2 points (moderate improvement at least in 2 functions or great improvement in 1 function) as the probable MCID.

Handgrip strength was assessed with a JAMAR dynamometer (Sammons Preston Rolyan, Bolingbrook, IL) following the recommendation of the American Society of Hand Therapists.

The EuroQoL-5 Dimensions (EQ-5D) is a generic health index of quality of life, that comprises a 5-part questionnaire and a visual analogic self-rating scale (VAS).[33] We calculated the EQ-5D health index by applying a weighting system previously validated, scoring from −0.59 (lower quality of life, worse than dead) to 1 (full health), and the VAS (0 to 100%).

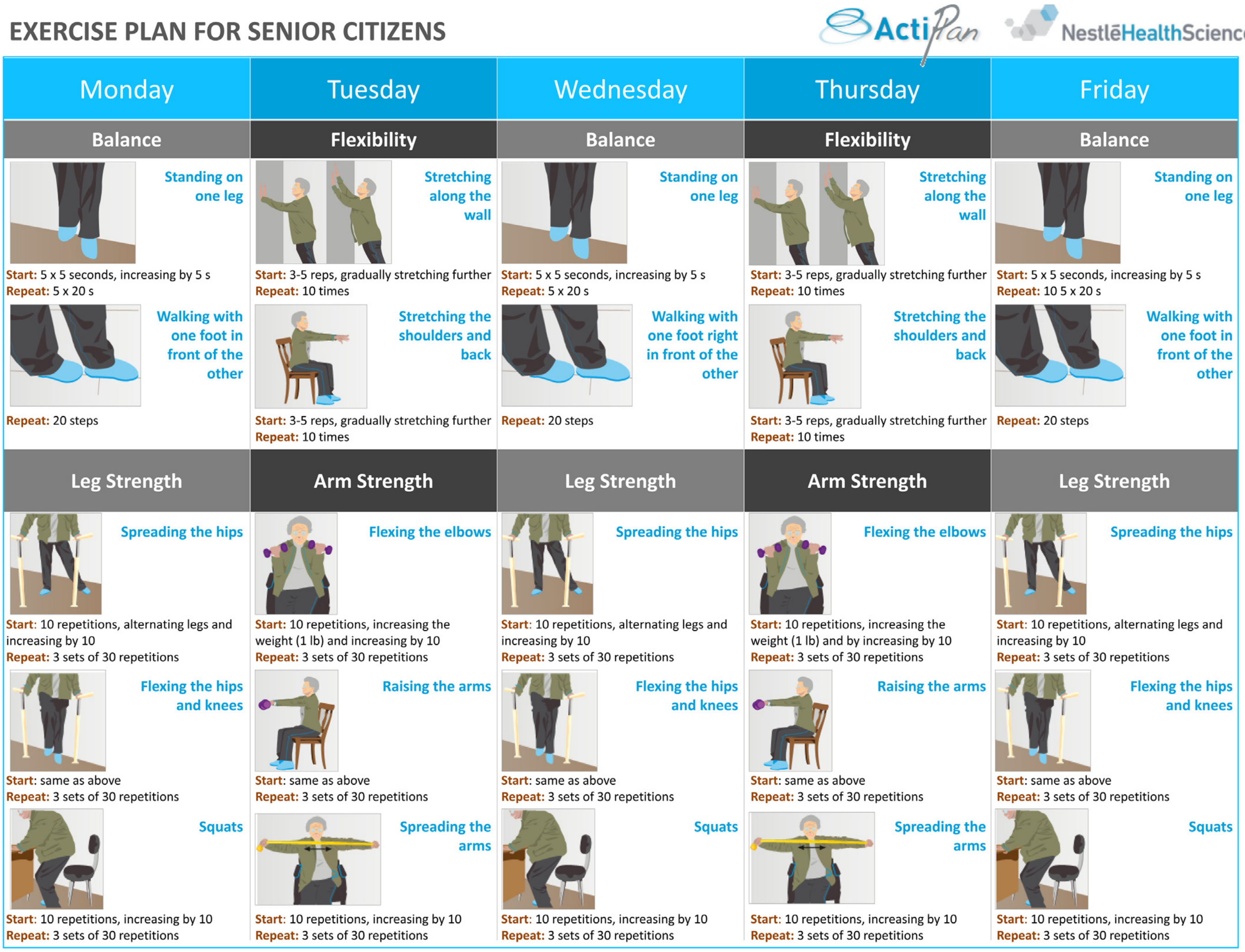

Fig. 1. ActiPlan in English.

Nutritional parameters: Weight (kg), height (cm), and body mass index (BMI; kg/m^2) were recorded. The Short-Form Mini Nutritional Assessment (MNA-SF) is a 6-item scale that assesses nutritional risk, ranging from 0 (poorer nutritional state) to 14 (better nutritional state). Malnutrition was considered with scores 0 to 7, nutritional risk with scores 8 to 11 and good nutritional state with scores 12 to 14. Bioimpedance analysis (BIA) also was conducted at 6 and 12 weeks of follow-up, determining fat mass (kg and %) and fat-free mass (FFM; kg). A blood sample was analyzed measuring total proteins (g/dL), albumin (g/dL), transferrin (mg/dL), cholesterol (mg/dL), vitamin D (ng/mL), and hemoglobin (g/dL).

Control Variables

At baseline, the following control variables were recorded: Age, sex, chronic diseases, and the Folstein Mini-Mental State Examination (MMSE).

Adherence to Intervention and Adverse Events

Daily adherence to physical exercise and ONS was assessed. Excellent adherence was considered when higher than 80% of the intervention planned, and good adherence when higher than 60%.

Nausea, vomiting, diarrhea, flatulence, constipation, and abdominal pain were monitored at 6- and 12-week follow-up. Serious adverse events during the study follow-up were death in 6 cases, and hospitalization in 3 cases, none of them related to the study intervention. Intervention had to be prematurely stopped in 5 cases. In 2 cases there was ONS intolerance, in 2 others there was physical exercise intolerance, and in 1 case there was intolerance to both interventions.

Ethics

The study was approved by the Ethics Committee of the Hospital Clínic i Provincial de Barcelona, March 8, 2012. Our investigation complies with the standards of the Helsinki declaration concerning investigation with human subjects. All participants signed an informed consent form before inclusion in the study.

Statistics

A descriptive analysis of the subjects' characteristics was performed using proportions and measures of central tendency and dispersion according to the nature of the variables. Subsequently, a bivariate analysis was performed using the paired Student t test to determine differences in functional, nutritional, quality of life, BIA, and blood parameter variables, between baseline and 6- and 12-week follow-up. The percentage of participants improving the MCID of functional tests was calculated. Pearson χ^2 tests (when frequency of cells was <5, the Fisher exact test was used) were used for determining the association between control variables and the presence of MCID of functional variables, at the 6- and 12-week follow-up. When control variables had 3 or more categories, linear per linear association also was analyzed to determine tendencies.

Last, we underwent a multivariant analysis with logistic regression models to describe the variables independently associated with MCID in SPPB. In the model we included age, sex, presence of 5 Fried frailty criteria, low vitamin D values, and BMI. This model classified correctly 80.6% of the study population.

All data were stored and analyzed using the SPSS 17.0 software program (IBM SPSS Statistics, IBM Corporation, Chicago, IL).

Results

The study flow chart is presented in Figure 2. A total of 91 residents participated in the study. At week 6, 80 participants remained in the study and 11 abandoned (12.1%), and at week 12, 69 completed the study and 22 had an early termination. The causes of early termination were death in 6 cases, patient desire in 4 cases, hospitalization in 3 cases, intervention stop in 5 cases (2 ONS stop, 2 physical exercise stop, and 1 both), and lost to follow-up in 4 cases. The baseline characteristics of those who abandoned the study (age, sex, nutritional status, functional status, chronic diseases, cognitive status, blood parameters, BIA, and quality of life) did not differ significantly from those who completed it.

Baseline characteristics of the complete sample, both in men and women, and of participants completing the study are presented in Table 1. The prevalence of at least 1 chronic disease was 98.9%, the more frequent pathologies were the following: cardiovascular (72.5%), neurologic/psychiatric (65.9%), musculoskeletal (60.4%), gastrointestinal/hepatic (45.1%), endocrine/metabolic (41.8%), genitourinary (29.7%), infectious (14.3), respiratory (14.3%), cancer (8.8%), and others (34.1%).

Adherence to ONS was higher than 80% in 62.6% of participants, between 60% and 80% in 20.9% of participants, between 40% and 60% in 8.8% of participants, between 20% and 40% in 1.1% of participants, and in 6.6% of participants data were not available. Adherence to physical exercise was higher than 80% in 93.4% of participants, between 60% and 80% in 4.4% of participants, between 40% and 60% in 1.1% of participants, and in 1.1% of participants data were not available. Regarding exercise intervention, 70.2% of patients followed the plan, and in 29.8% it was necessary to replace some exercises, most frequently squatting, walking in line, and standing on one leg.

The number of participants with secondary effects of ONS at week 6 and between weeks 6 and 12 were, respectively, nausea 5 (5.5%) and 2 (2.2%), vomiting 3 (3.3%) and 0 (0%), diarrhea 7 (7.7%) and 3 (3.3%), flatulence 13 (14.3%) and 5 (5.5%), constipation 8 (8.8%) and 3 (3.3%), and abdominal pain 7 (7.7%) and 1 (1.1%). Only 1 case of diarrhea at week 6, another one between weeks 6 and 12, and 1 case of flatulence at week 6 were considered of severe intensity.

Table 2 presents the evolution of functional, nutritional, quality of life, BIA, and main blood sample parameters between baseline and 6 and 12 weeks of follow-up. Mean improvement in SPPB at week 6 was 0.8 points, and in SF-LLFDI 3.1 points. Although there was no significant improvement in function at week 12, mean values were higher at that point than at baseline. Participants improved their quality of life at week 6, measured with the EQ-5D index and EQ-5D VAS, and at 12 weeks measured with the EQ-5D VAS. Moreover, participants improved their nutritional status; weight gain, BMI increase, and higher MNA-SF scores were recorded at the 6- and 12-week follow-up. Regarding blood parameters, only vitamin D and transferring increased at week 12.

At week 6, 48 participants (52.7%) improved SPPB at least 1 point (MCID), and 44 (48.4%) did so at week 12. Regarding SF-LLFDI, 39 participants (42.9%) improved at least 2 points at week 6, and 46 (50.5%) at week 12.

Table 3 presents the association between the main control variables and the presence of MCID in functional tests at the 6- and 12-week follow-up. Participants had greater probability of improving functional status measured with the SPPB and SF-LLFDI when they presented with lower baseline SPPB scores, lower baseline BMI, lower vitamin D levels, and more baseline frailty criteria.

Table 4 presents multivariate analysis between control variables and functional improvement measured with the SPPB. The presence of 5 Fried frailty criteria was independently associated with better functional outcomes, and lower vitamin D levels with improvement in SPPB at week 6.

Participants with low baseline vitamin D levels presented significant improvement in function at 6 weeks, but there was no increase in FFM between baseline and 12-week follow-up in the complete

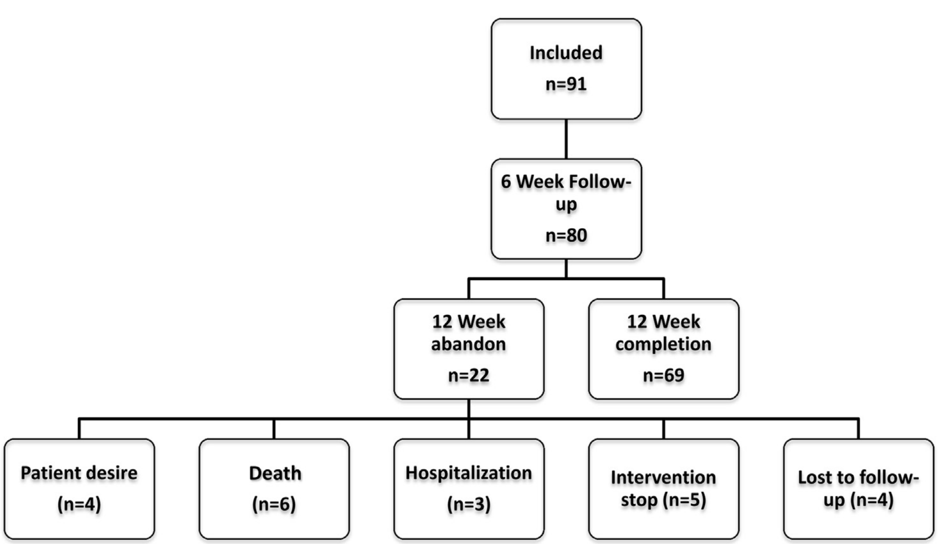

Fig. 2. Study flow chart.

Table 1
Baseline Characteristics of the Sample

Variable	All Sample, n = 91	Male, n = 27	Female, n = 64	Completing Study, n = 69
Age, y	85.6 (5.6)	83.9 (5.7)	86.3 (5.4)	85.8 (5.5)
Body weight, kg	59.9 (12.3)	64.8 (9.7)*	57.8 (12.7)*	59.7 (11.8)
Usual weight, kg	62.2 (11.7)	67.7 (9.4)†	59.8 (11.9)†	62.1 (11.7)
Fat mass, %	28.9 (9.1)	24.9 (7.9)†	30.6 (9.1)†	29.6 (9.6)
Fat mass, kg	17.8 (8.1)	16.5 (7.2)‡	18.3 (8.5)‡	18.2 (8.5)
FFM, kg	41.9 (7.6)	48.0 (6.3)	39.3 (6.5)	41.3 (7.2)
MNA-SF mean	10.2 (2.4)	10.3 (2.6)	10.2 (2.4)	10.3 (2.3)
12–14	37 (40.7)	9 (33.3)	28 (43.8)	27 (39.1)
8–11	39 (42.9)	14 (51.9)	25 (39.1)	32 (46.4)
0–7	14 (15.4)	4 (14.8)	10 (15.6)	9 (13.0)
BMI mean, kg/m^2	26.4 (5.1)	25.8 (3.9)	26.6 (5.5)	26.5 (4.8)
<18.5	2 (2.2)	0 (0.0)	2 (3.1)	1 (1.4)
18.5–24.9	39 (42.9)	12 (44.4)	27 (42.2)	28 (40.6)
25–29.9	30 (33.0)	11 (40.7)	19 (29.7)	26 (37.7)
≥30	20 (22.0)	4 (14.8)	16 (25.0)	14 (20.3)
<23	27 (29.7)	7 (25.9)	20 (31.3)	18 (26.1)
≥23	64 (70.3)	20 (74.1)	44 (68.8)	51 (73.9)
Frailty criteria				
Weight loss	52 (57.1)	19 (70.4)	33 (51.6)	40 (58.0)
Exhaustion	84 (92.3)	25 (92.6)	59 (92.2)	64 (92.8)
Slowness	88 (96.7)	26 (96.3)	62 (96.9)	67 (97.1)
↓Physical activity	82 (90.1)	24 (88.9)	58 (90.6)	64 (92.8)
Weakness	69 (75.8)	18 (66.7)	51 (79.7)	55 (79.7)
3 Criteria	25 (27.5)	9 (33.3)	16 (25.0)	16 (23.2)
4 Criteria	30 (33.0)	5 (18.5)	25 (39.1)	23 (33.3)
5 Criteria	36 (39.6)	13 (48.1)	23 (35.9)	30 (43.5)
Grip strength, kg	16.2 (7.4)	20.5 (7.9)‡	14.3 (6.3)‡	16.0 (6.8)
SPPB	6.8 (2.8)	6.8 (2.7)	6.8 (2.9)	6.7 (2.9)
SF-LLFDI	46.9 (12.8)	47.5 (13.6)	46.6 (12.6)	46.3 (13.1)
EQ-5D index	0.58 (0.22)	0.61 (0.23)	0.57 (0.21)	0.59 (0.23)
EQ-5D VAS	59.6 (21.0)	58.4 (24.1)	60.1 (19.7)	59.1 (22.0)
MMSE	21.6 (6.3)	24.3 (5.3)*	20.6 (6.4)*	21.8 (5.9)

Note: All data are mean (standard deviation) or number of participants (percentage).
*$P < .05$.
†$P < .01$.
‡$P < .001$.

Table 2
Evolution of Outcome Variables at 6- and 12-Week Follow-up

	Baseline to 6-wk Means (Mean Difference; 95% CI)	Baseline to 12-wk Means (Mean Difference; 95% CI)
Function		
SPPB	6.8–7.6 (0.8; 0.5–1.1)‡	6.7–6.8 (0.1; −0.7–1.0)
SF-LLFDI	46.5–49.6 (3.1; 1.8–4.4)‡	46.8–47.6 (0.8; −2.3–3.8)
Grip strength, kg	15.5–16.0 (0.5; −0.5–1.5)	16.5–17.1 (0.6; −0.5–1.6)
EQ-5D		
EQ-5D index	0.58–0.62 (0.04; 0.01–0.07)*	0.58–0.59 (0.00; −0.06–0.06)
EQ-5D VAS	60–66 (6; 3–10)†	59–64 (5; 0–10)*
Nutrition		
Weight, kg	59.9–60.7 (0.8; 0.3–1.2)†	59.9–61.6 (1.7; 0.9–2.5)‡
BMI, kg/m^2	26.4–26.8 (0.4; 0.2–0.6)‡	26.5–27.3 (0.8; 0.4–1.2)‡
MNA-SF	10.1–11.5 (1.4; 0.9–1.9)‡	10.3–11.1 (0.8; 0.1–1.5)*
BIA		
FFM, kg	42.2–42.5 (0.3; −0.6–1.2)	41.4–41.3 (−0.1; −1.1–1.0)
Fat mass, kg	18.7–20.3 (1.6; −0.5–3.6)	17.6–19.1 (1.5; 0.5–2.4)†
Fat mass, %	29.8–30.5 (0.7; −0.5–1.9)	29.1–31.0 (1.9; 0.5–3.3)†
Blood parameters		
Albumin, g/dL	—	3.7–3.8 (0.1; −0.1–0.2)
Total proteins, g/dL	—	6.7–6.6 (−0.1; −0.4–0.2)
Vitamin D, ng/mL	—	17.4–25.3 (7.9; 5.0–10.8)‡
Parathormone, pg/mL	—	53.5–53.8 (0.3; −6.5–7.0)
Hemoglobin, g/dL	—	13.0–13.4 (0.4; 0.0–0.7)
C-reactive protein, mg/dL	—	3.6–4.3 (0.7; −0.6–2.2)
Transferrin, mg/dL	—	235–248 (13; 0.8–25.0)*
Total cholesterol, mg/dL	—	177–178 (1; −7–8)

Note: Dashes represent non available data. Blood parameters were not determined at 6-week follow-up.
*$P < .05$.
†$P < .01$.
‡$P < .001$.

Table 3
Association Between Control Variables and Minimal Clinical Significant Improvement in Functional Outcomes at 6- and 12-Week Follow-up

	SPPB 6-wk, Improvement 1 Point, n (%)	SPPB 12-wk, Improvement 1 Point, n (%)	SF-LLFDI 6-wk, Improvement 2 Points, n (%)	SF-LLFDI 12-wk, Improvement 2 Points, n (%)
Baseline SPPB				
0–3	6 (66.7)†	9 (100)	7 (87.5)‡	8 (88.9)*
4–7	28 (77.8)†	24 (75.0)	19 (59.4)‡	22 (62.9)*
8–12	14 (40.0)†	11 (39.3)	13 (44.8)‡	16 (45.7)*
Baseline BMI, kg/m^2				
<18.5	1 (100)*	1 (100)*	1 (100)‡	1 (100)
18.5–24.9	26 (76.5)*	22 (78.6)*	18 (66.7)‡	21 (61.8)
25–29.9	14 (51.9)*	16 (61.5)*	16 (59.3)‡	16 (59.3)
≥30	7 (38.9)*	5 (35.7)*	4 (28.6)‡	8 (47.1)
Frailty criteria				
3	9 (42.9)†	10 (62.5)	6 (35.3)*	7 (33.3)*
4	12 (48.0)†	11 (47.8)	11 (50.0)*	14 (58.3)*
5	27 (79.4)†	23 (76.7)	22 (73.3)*	25 (73.5)*
Vitamin D				
<20 ng/mL	39 (67.2)*	12 (63.2)	30 (60.0)	34 (59.6)
≥20 ng/mL	9 (40.9)*	32 (64.0)	9 (47.4)	12 (54.5)

*$P < .05$.
†$P < .01$.
‡Linear per linear association $P < .05$.

sample. However, participants with vitamin D levels lower than 20 ng/mL had a decrease in FFM of 0.62 kg, whereas those with higher vitamin D levels had an increase of 1.23 kg (difference 1.85, 95% confidence interval [CI] −0.31–4.19; $P = .09$) at week 12.

Discussion

The main result of our study is that an intervention with a HP/HC ONS with vitamin D and calcium plus physical exercise, in frail institutionalized older adults, improved functional status at 6 weeks, nutritional status at weeks 6 and 12, and quality of life at weeks 6 and 12. To our knowledge, this is the first intervention study conducted specifically in frail institutionalized older adults with a mixed nutritional and exercise intervention.

Interestingly, our study also identified older adults with higher probability of improving their functional status. Those with lower BMI, lower previous physical function, higher number of frailty criteria, and lower vitamin D levels had an independent association with functional improvement. This is in agreement with previous studies demonstrating the benefits of low-to medium-intensity exercise and nutrition interventions in this targeted population.[15,34]

Frailty is a common condition in institutions, as has been demonstrated in recent studies,[4–8] and has been independently associated with mortality and disability in this population.[13] However, it is still not known if valid interventions for frail community-dwelling older adults could be valid for nursing home populations, due to their special characteristics with high rates of disability, multimorbidity, and geriatric syndromes. Our study adds to previous research that it is possible to identify and recruit frail older people for clinical studies, and that treating frailty in older people is a realistic therapeutic goal. The good results observed, even though residents were rather very frail individuals, suggest the need to reinforce nutrition and exercise interventions in prefrail and community-dwelling frail older adults, rather than wait for patients to be institutionalized due to higher dependency.

It is of interest that only 15.4% of our sample had malnutrition using the MNA-SF, 42.9% were at risk of malnutrition, and 40.7% were well-nourished, and that all of them were treated with ONS. The rationale for this intervention was based on ESPEN guidelines,[14] and we need to state that we were not only treating malnutrition, but treating frailty. Even though ESPEN recommendations regarding frailty and ONS is correct to maintain or improve nutritional status, the results of our study suggest the possibility of extending the recommendation of combined ONS and physical exercise to improve frailty standards of care beyond current usual clinical practice. We could not analyze the individual effect of nutritional supplementation and exercise on the outcome variables, because our intervention was designed as a global combined approach. Recent ongoing studies in community-dwelling frail older adults also are incorporating this approach.[35]

Physical frailty is a state of reduced physiological reserve associated with an increased vulnerability leading to disability. Poor nutritional status, low protein intake, low physical activity, and low vitamin D levels have been identified among other pathophysiologic factors leading to frailty,[36] and multidomain interventions have been proposed for its treatment, including nutrition and physical exercise.[37] Because physical inactivity and dietary inadequacies are among the main contributors,[27] it seemed appropriate to focus the actual investigation primarily on these risk factors. Our positive results could have been achieved through an increase of vitamin D levels, an

Table 4
Models to Determine Independent Association Between Control Variables and Functional Outcomes at 6- and 12-Week Follow-up

	SPPB 6-wk, Improvement 1 Point, OR (95% CI)	SPPB 12-wk, Improvement 1 Point, OR (95% CI)	SF-LLFDI 6-wk, Improvement 2 Points, OR (95% CI)	SF-LLFDI 12-wk, Improvement 2 Points, OR (95% CI)
Age, y	0.99 (0.90–1.09)	0.97 (0.87–1.07)	1.03 (0.94–1.14)	1.14 (1.03–1.26)†
Female sex	1.58 (0.51–4.92)	1.57 (0.50–4.93)	0.69 (0.22–2.14)	0.71 (0.23–2.14)
5 Frailty criteria	3.94 (1.28–12.13)*	2.18 (0.71–6.72)	3.17 (1.06–9.48)*	3.22 (1.10–9.43)*
BMI, kg/m^2, <25	2.55 (0.86–7.51)	2.97 (0.91–9.68)	1.37 (0.45–4.22)	0.86 (0.30–2.48)
Vitamin D, ng/mL, <20	3.32 (1.05–10.52)*	0.88 (0.27–2.88)	1.59 (0.51–4.99)	0.96 (0.32–2.87)

OR, odds ratio.
*$P < .05$.
†$P < .01$.

increase in muscle synthesis, an improvement of strength and balance, an increase of other nutritional elements, or a combination of all of them. We could only demonstrate an increase of vitamin D levels, an increase in grip strength, and an increase in nutritional status, although it is not possible to exclude the participation of the other factors, or the relative individual importance of all of them.

Regarding blood sample parameters, we could only demonstrate a significant increase in vitamin D and transferring between baseline and 12-week follow-up, and a nonsignificant increase in hemoglobin. Participants were mostly deficient in vitamin D levels, and intervention showed to be effective at increasing their levels. However, there was no increase in total proteins, albumin, and cholesterol. Possibly, participants did not need to compensate these parameters because at baseline they were in normal levels, as shown in Table 2.

Function was improved without an increase in FFM, but with an increase in vitamin D levels. Vitamin D status is positively associated with muscle strength and physical performance and inversely associated with risk of falling, and clinical trials of vitamin D supplementation in older adults with low vitamin D status mostly report improvements in muscle performance and reductions in falls. The underlying mechanisms are probably both indirect via calcium and phosphate and direct via activation of the vitamin D receptor on muscle. This activation at the genomic level regulates transcription of genes involved in calcium handling and muscle cell differentiation and proliferation, thus increasing muscle fiber size and number. Moreover, vitamin D has shown to improve muscle function and contraction.[38,39] In our study, although participants with low vitamin D values presented a better improvement in function, only participants with vitamin D values over 20 ng/mL showed FFM increase. High-range vitamin D increase could be necessary for increasing fiber size and number, while increases in the lower range could improve muscle function.

The rationale for using ONS instead of properly introducing the micronutrients (proteins, calcium, vitamin D, and fiber) separately is multifactorial. First, it is easier for frail older adults to have 1 single product intake than using different products for each compound. Second, for study precision, ONS allows the exact quantification of all micronutrient intake in a frail population with difficulties in complementing a normal oral diet. Third, it has been recently described that managing several patient populations suffering from or at risk of disease-related malnutrition in different health care settings with ONS seems to be an efficient intervention from a health economic perspective, in most cases even leading to cost savings.[40]

Probably the most important limitation of our study is the absence of a control group. However, we think that there is enough evidence to consider bad practice an intervention on frail older adults not including physical exercise and nutrition actions. It could be argued that a dietary intervention without ONS could have been appropriate. However, our intervention not only allowed the quantification of nutritional intake including kilocalories, proteins, fiber, calcium, and vitamin D, but also allowed the possibility of monitoring adherence. This is important in a frail population usually characterized by low nutritional intake.[41] In keeping with studies of this type, it was not possible to blind participants and treating clinicians to the intervention, making feasible a participation bias. However, database treatment and statistical analysis were blinded, and the study Promotor did not take part in any of these study processes. We also decided that our main outcome function variables had to meet 2 characteristics: First, we needed a performance-based measure that could reduce observer bias, and second, we needed a scale with low ceiling and floor effects. These were the reasons for choosing SPPB and SF-LLFDI. Although our study was multicentric, more centers from more countries, from different types of institutions and with a larger sample, could be of interest for confirming our results.

The study follow-up was short, 12 weeks, and follow-up beyond this time could have been of interest, especially after the observed decline in function between 6 and 12 weeks. We must remark that our population was very old and very frail, with chronic diseases, and different rates of disability, so we could expect a naturalistic decline in function at 12 weeks without intervention. Recently, Slaughter et al[42] found a 5.9% decrease in physical function measured with the functional independence measure instrument at 6 months in an urban cohort of nursing home older adults with dementia, independent for transferring (mean age 86.1, SD 7.1). Our population had higher outcome scores at 12 weeks than baseline, making feasible a global improvement compared with a nonintervention population of similar characteristics.

The study was conducted in a country with well-developed health and care services for older adults, the clinical teams involved had considerable experience in nursing home health care, physiotherapists were involved in the exercise plan, and adherence was strictly monitored. However, it should be of interest to generalize the intervention to other situations with different health and care services.

Conclusions

A 12-week intervention with ONS plus physical exercise improves function, nutritional status, and quality of life in frail institutionalized older adults. This improvement is higher in participants with more frailty criteria, lower functional level, lower vitamin D levels, and with poorer nutritional status.

More than 90% of residents accomplished daily exercises, and more than 80% accomplished with an oral intake of more than 60% of ONS.

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